II. REMARKS

Claims 1-5, 12, 13, 24 and 25 are pending and stand variously rejected under 35 U.S.C. 112, first and second paragraphs. Applicants appreciate the Examiner's acknowledgment that the claims are patentable over the prior art of record.

By amendment herein, claim 1 is now directed to a method that generates an immunological response to an intracellular pathogen. Support for this amendment can be found throughout the specification and original claims, for example, on page 8, lines 35-37; page 12, line 11, and the last line of original claim 1. Claims 5 and 25 have been amended to correct typographical errors and provide proper antecedent basis. The amendments are made solely to expedite prosecution, are not intended in any way as an acknowledgment as to the correctness of the Examiner's position, and are made for reasons unrelated to patentability.

Submitted herewith is a Supplement IDS and appropriate fee.

In view of the foregoing amendments and following remarks, reconsideration of the claims is respectfully requested.

35 U.S.C. § 112, First Paragraph

Claims 1-5, 12-13, and 24-25 stand rejected under 35 U.S.C. § 112, first paragraph as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. In support of the rejection, the Examiner maintains that Applicants "have provided no evidence in the unpredictable gene therapy art that the immune response generated reaches therapeutic threshold levels *in vivo*." (See, Office Action mailed 2/2/01, page 5).

Before addressing each issue raised by the Office, Applicants note the test of enablement is whether one reasonably skilled in the art could make or use the invention from the disclosures in the patent coupled with information known in the art without

undue experimentation. *Ex parte Forman*, 230 USPQ 546 (BPAI 1986). Whenever the PTO makes a rejection for failure to teach how to make and/or use the invention, the PTO must explain its reasons for the rejection and support the rejection with (i) acceptable evidence, or (ii) reasoning which contradicts the Applicants' claim: the reasoning must be supported by current literature as a whole and the PTO must prove the disclosure requires undue experimentation. *In re Marzocchi*, 439 F.2d 220, 223-24, 169 USPQ 367, 369-70 (CCPA 1971). For the reasons detailed below, the Office has failed to establish a *prima facie* case of non-enablement.

Applicants also note that is well-settled that the enablement requirement is satisfied if the applicant's specification teaches one of skill in the art how to make and use the claimed invention without undue experimentation. *In re Wands,* 8 USPQ2d 1400 (Fed. Cir. 1988). Further the "invention" referred to in the enablement requirement of section 112 is the claimed invention." *See, Christianson v. Colt Industries Operating Corp.* 3 USPQ2d 1241 (Fed. Cir. 1987), emphasis added. Thus, the Office must first determine what each claim recites when the claim is considered as a whole, not when its parts are analyzed individually. See, Training Manual on Enablement, page 9. Moreover, the existence of inoperative or ineffective embodiments does not mean that the enablement requirement if not satisfied. Indeed, if any use of multiple uses disclosed in the specification are enabled, the application is enabling. See, Training Manual, page 21.

In the pending case, the Office acknowledges that the claims are enabled for the construction of various vectors and for the generation of an immune response following administration of certain gene delivery vehicles. (Office Action mailed 2/2/01, page 5). However, in support of the enablement rejection, the Examiner cites numerous references allegedly showing the unpredictability of gene therapy (citing Verma and Marshall) and the unpredictability of gene therapy using alphaviral vectors (citing Frolov, Ohno and Garoff).

As a threshold matter, Applicants note that the pending do not recite methods of

"treating" intracellular pathogens (*e.g.*, HIV). Rather, they are drawn to methods of generating an immunological response to intracellular pathogens. The specification indicates that the claimed methods provide "an effective means of inducing potent class I-restricted protective and therapeutic CTL responses, as well as humoral responses." (*See, e.g.*, page 8, lines 36-37). As is well-known, an immunological response can be either a humoral immune response (*e.g.*, mediated by antibodies) or a cellular immune response (*e.g.*, mediated by T-lymphocytes and/or other white blood cells). Therefore, when properly interpreted in light of the specification, the pending claims are directed to methods of eliciting cellular and humoral immune responses and the enablement requirement is satisfied by Applicants' showing that these methods elicit both humoral and cellular immune responses. (See, Examples).

Furthermore, Applicants submit that the Office cannot reject the claims on the basis that one "implied" use may be ineffective or inoperative. In other words, the fact that the enabled cellular and humoral immune responses may or may not be protective and/or therapeutic is not relevant to the enablement inquiry in this case. As noted above, all that is required to satisfy enablement is that specification enable one use. *See, e.g., In re Angstadt,* 190 USPQ 214 (CCPA 1976). In the case at hand, there is no dispute that Applicants have enabled methods of eliciting cellular and humoral immunological responses to intracellular pathogens. Thus, Applicants have plainly shown how to make and use the claimed invention. Accordingly, Applicants are not required to establish whether these immunological responses are protective or therapeutic. In sum, Applicants' specification fully enables the pending claims by enabling not only a single use, but by enabling the claims throughout their scope.

Applicants also traverse the Examiner's assertion that the gene therapy references "established the unpredictability of using alphavirus vectors for transferring exogenous DNA *in vivo.*" (Frolov, Ohno and Garoff cited on page 3 of the Office Action). These references do no such thing. None of these reference address using alphavirus vectors to

generate an immune response to an intracellular pathogen and, indeed, these references indicate that alphavirus is a suitable gene delivery vehicle. Frolov notes that "recombinant alphavirus RNA replicons may also facilitate genetic vaccination and transient gene therapy." (Frolov, page 11371, left column). Garoff notes that "alphavirus vectors have established themselves as convenient tools to obtain efficient gene expression in a wide range of host cells." (Garoff page 464, left column). Ohno is directed to cell-specific targeting of alphavirus vectors. Thus, at best, the references cited by the Office all evidence that, prior to Applicants' invention, there was a need for improved methods of generating immune responses using alphavirus vectors. This is a far cry from establishing that methods of eliciting cellular and humoral responses using alphavirus vectors are not enabled by Applicants' specification. In fact, Applicants' specification describes and demonstrates the generation of an immune response against an intracellular pathogens such as HCV and HIV. Thus, for the reasons of record and those detailed herein, the various gene therapy references are not relevant to the claimed invention and certainly do not establish unpredictability of the claimed invention.

In the pending case, the Office has not pointed to the methodologies to practice methods of which allegedly are unpredictable and not within the purview of a skilled artisan. Accordingly, pursuant to 37 C.F.R. 1.104(d)(2), Applicants request that the rejection be supported by references or Examiner affidavits so that Applicants can have a full and fair opportunity to respond.

Despite the failure of the Office to make a case for non-enablement, Applicants address why the claims are enabled throughout their scope. As previously discussed, enablement is fact-dependent. The standards articulated in *In re Wands* can be used to help determine whether the specification at issue is in fact enabling. Indeed, the situation in *Wands* is highly analogous to that at hand. In *Wands,* the Federal Circuit held that claims to generic monoclonal antibodies were enabled by a specification that taught the entire procedure of making monoclonal antibodies. Moreover, in view of the high level

of skill in the art and routine nature of each step of the antibody-making procedure, the court held that the amount of experimentation required to make other monoclonals was extensive, but not undue.

Similarly, in the pending case, Applicants submit that their specification clearly sets forth the procedure for determining dosage levels, routes of administration of vectors and proteins as well as selection and administration of DNA sequences. Applicants direct the Examiner's attention to Examples 1-3, where the preparation of polynucleotides encoding antigens (*e.g.*, from the core region) of a viral polyprotein are described. Administration is described, for example, on page 25, line 36 to page 26, line 29 as well as in Examples 11 and 14. The specification describes how to assess the immunological and/or therapeutic effects, for example by biochemical or cytotoxicity analyses. (See, *e.g.*, Examples 12, 13, 15 and 16). Similarly, with respect to determining appropriate DNA sequences encoding antigens from intracellular pathogens, one skilled in the art could readily determine, in view of the teachings of Applicants' specification of how to select and use suitable nucleotide sequences. The entire genome of many intracellular pathogens has been sequenced. (*see, e.g.*, page 10 and citations therein). Although certainly not required to establish enablement, multiple working examples regarding selection of sequences, promoters, dosages and routes of administration are also provided in the specification. It is axiomatic that an applicant does not need to specify the dosage or method of use if it is known to one of skill in the art that such information could be readily obtained. *See, e.g.*, USPTO Training Materials on Enablement, page 20. In fact, a considerable amount of routine experimentation is permissible if the specification provides a reasonable amount of guidance, with respect to the direction in which experimentation should proceed, to enable the determination of how to practice a desired embodiment of the claimed invention. *Ex parte Forman, supra*; *In re Wands*, 858 F.2d 731, 8 USPQ2d 1400 (Fed. Cir. 1988). Thus, Applicants submit that there is more than sufficient guidance as to the claimed methods in the specification.

In sum, when the factors in *Wands* are weighed, it would not require undue experimentation to practice the claimed invention, given the guidance found in the specification and state of the art. The claimed invention is, therefore, fully enabled by the specification and Applicants respectfully request the rejections under 35 U.S.C. § 112, first paragraph be withdrawn.

35 U.S.C. § 112, Second Paragraph

Claims 1-5, 12-13 and 24-25 stand rejected under 35 U.S.C. § 112, second paragraph as allegedly indefinite. In particular, the Examiner makes the following five allegations:

(1) Claim 1 is alleged to be incomplete as it does not provide a positive process step that relates back to the preamble of the claim. In view of the foregoing amendments to claim 1, this objection has been obviated.

(2) The term "derived" in claim 1 is alleged to be indefinite. Although Applicants submit that the term "derived" was sufficiently definite, claim 1 has been amended herein to specify that the antigen is "obtained from" an intracellular pathogen, as indicated for example on page 4, line 1 and line 29. Both the terms "derived from" and "obtained from" include immunogenic portions that have been isolated, selected and/or modified. (See, page 15, lines 29-30; page 16, line 3).

(3) Claim 1 is allegedly indefinite because it is unclear whether the immunogenic portion of an antigen administered in step(b) needs be the same the protein encoded by the sequence used in step (a). Applicants submit that the claims, when read in light of the specification, are amply clear. For instance, the specification is clear that the methods include administering a protein "which comprises the afore-mentioned immunogenic portion." (See, page 3, line 30). Additionally, Applicants' specification notes that "various immunogenic portions of the above described antigens may be combined in order to present an immune response." (See, page 11, lines 15-17). It is also clear from

the specification that at least one of the proteins administered in step (b) corresponds to at least one of the immunogenic portions encoded by the polynucleotide. (See, *e.g.*, page 17, line 1). In other words, the claims are clear that step (b) involves the administration of at least one protein that corresponds to at least one of the immunogenic portions encoded by the polynucleotide administered in step (a). In view of the foregoing, Applicants submit that the claims are sufficiently definite and respectfully request withdrawal of the rejections.

(4) Claim 5 is allegedly indefinite because the phrase viral antigen lacks antecedent basis. Applicants appreciate the Examiner's suggestion to amend claim 5 to depend from claim 4 and have incorporated this suggestion by amendment herein. Accordingly, this rejection has been obviated.

(5) Claim 25 is allegedly indefinite for reciting a "composition" instead of a "method." Applicants have corrected the typographical error by amendment herein, thereby obviating the rejections.

In view of the foregoing amendments and remarks, Applicants submit that the rejections have been obviated or otherwise overcome and, accordingly, request that the rejections under Section 112, second paragraph be withdrawn.

III. CONCLUSION

In view of the foregoing amendments, Applicants submit that the claims are now in condition for allowance and request early notification to that effect.

The Commissioner is hereby authorized to charge any fees under 37 C.F.R. §§ 1.16 and 1.17 which may be required by this paper, or to credit any overpayment, to Deposit Account No. 18-1648.

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PATENT

Please direct all further communications regarding this application to:

Anne S. Dollard, Esq.
CHIRON CORPORATION
Intellectual Property - R440
P.O. Box 8097
Emeryville, CA 94662-8097
Telephone: (510) 923-2708
Facsimile: (510) 655-3542.

Respectfully submitted,

Date: 10 April 2002 By: Dhas Pasternak

Dahna S. Pasternak
Registration No. 41,411

CHIRON CORPORATION
Intellectual Property - R440
P.O. Box 8097
Emeryville, CA 94662-8097
Telephone: 510-923-2708
Facsimile: 510-655-3542

Version Showing Changes Made

1. (Amended) A method for [treating] generating an immune response against one or more intracellular [infections] pathogens within warm-blooded animals, comprising:

(a) administering to a warm-blooded animal a gene delivery vehicle comprising a polynucleotide encoding at least one immunogenic portion of an antigen [derived] obtained from an intracellular pathogen; and

(b) administering to said warm-blooded animal [a] at least one protein which comprises at least one of said immunogenic portion of said antigen, such that an immune response again the intracellular pathogen is generated.

3. (Amended) The method according to claim 1, wherein said protein is administered prior to administration of said [vector construct] gene delivery vehicle.

5. (Amended) The method according to claim 3, wherein said viral antigen is obtained from a virus selected from the group consisting of hepatitis, feline immunodeficiency virus (FIV), and human immunodeficiency virus (HIV) [HIV].

11. (Amended) The method according to claim 1, wherein said [vector construct] gene delivery vehicle is [carried by] a recombinant retrovirus.

12. (Amended) The method according to claim 1, wherein said [vector construct is carried by a recombinant virus] gene delivery vehicle is selected from the group consisting of alphaviruses, adeno-associated virus and parvovirus.

13. (Amended) The method according to claim 1, wherein said [vector construct] gene delivery vehicle is a nucleic acid expression vector, or a eukaryotic layered vector initiation system.

14. (Amended) A composition. comprising a [vector construct which directs the expression of] gene delivery vehicle comprising a polynucleotide encoding at least one immunogenic portion of an antigen derived from an intracellular pathogen, a protein which comprises said immunogenic portion of said antigen, and a pharmaceutically acceptable carrier or diluent.

17. (Amended) The composition according to claim 16, wherein said viral antigen is obtained from a virus selected from the group consisting of hepatitis, feline immunodeficiency virus (FIV), and human immunodeficiency virus (HIV) [HIV].

23. (Amended) The composition according to claim 1, wherein said [vector construct is carried by] gene delivery vehicle is a recombinant retrovirus.

24. (New) The method of claim 1, wherein the gene delivery vehicle comprises naked DNA.

25. (New) The composition of claim 1, wherein the gene delivery vehicle comprises naked DNA.

Currently Pending Claims

1. (Amended) A method for generating an immune response against one or more intracellular pathogens within warm-blooded animals, comprising:

(a) administering to a warm-blooded animal a gene delivery vehicle comprising a polynucleotide encoding at least one immunogenic portion of an antigen obtained from an intracellular pathogen; and

(b) administering to said warm-blooded animal at least one protein which comprises at least one of said immunogenic portion of said antigen, such that an immune response against the intracellular pathogen is generated.

2. The method according to claim 1, further comprising the step of administering an immunomodulatory cofactor.

3. (Amended) The method according to claim 1, wherein said protein is administered prior to administration of said gene delivery vehicle.

4. The method according to claim 1, wherein said intracellular pathogen is virus and said antigen a viral antigen.

5. (Amended) The method according to claim 4, wherein said viral antigen is obtained from a virus selected from the group consisting of hepatitis, feline immunodeficiency virus (FIV), and human immunodeficiency virus (HIV).

6. The method according to claim 5, wherein said antigen is a hepatitis B antigen.

7. The method according to claim 6, wherein said hepatitis B antigen is selected from the group consisting of HBeAg, HBcAg and HbsAg.

8. The method according to claim 5 wherein said antigen is a hepatitis C antigen.

9. The method according to claim 8 wherein said hepatitis C antigen is selected from the group consisting of core antigen C, E 1, E2/NS1, NS2, NS3, NS4 and NS5.

10. The method according to claim 1, wherein said intracellular pathogen is a parasite.

11. (Amended) The method according to claim 1, wherein said gene delivery vehicle is a recombinant retrovirus.

12. (Amended) The method according to claim 1, wherein said gene delivery vehicle is selected from the group consisting of alphaviruses, adeno-associated virus and parvovirus.

13. (Amended) The method according to claim 1, wherein said gene delivery vehicle is a nucleic acid expression vector, or a eukaryotic layered vector initiation system.

14. (Amended) A composition. comprising a gene delivery vehicle comprising a polynucleotide encoding at least one immunogenic portion of an antigen derived from an intracellular pathogen, a protein which comprises said immunogenic portion of said antigen, and a pharmaceutically acceptable carrier or diluent.

15. The composition according to claim 14, further comprising an imunomodulatory cofactor.

16. The composition according to claim 14, wherein said intracellular pathogen is a virus, and said antigen a viral antigen.

17. (Amended) The composition according to claim 16, wherein said viral antigen is obtained from a virus selected from the group consisting of hepatitis, feline immunodeficiency virus (FIV), and human immunodeficiency virus (HIV).

18. The composition according to claim 16, wherein said antigen is a hepatitis B antigen.

19. The composition according to claim 18, wherein said hepatitis B antigen is selected from the group consisting of HBeAg, HBcAg and HbsAg.

20. The composition according to claim 16, wherein said antigen is a hepatitis C antigen.

21. The composition according to claim 20, wherein said hepatitis C antigen is selected from the group consisting of core antigen C, El, E2/NS1, NS2, NS3, NS4 and NS5.

22. The composition according to claim 14, wherein said intracellular pathogen is a parasite.

23. The composition according to claim 1, wherein said gene delivery vehicle is a

recombinant retrovirus.

23. (Amended) The composition according to claim 1, wherein said gene delivery vehicle is a recombinant retrovirus.

24. The method of claim 1, wherein the gene delivery vehicle comprises naked DNA.

25. (Amended) The method of claim 1, wherein the gene delivery vehicle comprises naked DNA.